**PCT** WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/135 — A1

(11) International Publication Number: WO 98/13033

(43) International Publication Date: 2 April 1998 (02.04.98)

(21) International Application Number: PCT/EP97/05034

(22) International Filing Date: 15 September 1997 (15.09.97)

(30) Priority Data:
9619962.5 25 September 1996 (25.09.96) GB

(71) Applicant *(for all designated States except US)*: KNOLL AKTIENGESELLSCHAFT [DE/DE]; Knollstrasse, D-67061 Ludwigshafen (DE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: KELLY, Peter, Finian [IE/GB]; E50 Pennyfoot Street, Nottingham NG1 1GF (GB). JONES, Stephen, Paul [GB/GB]; E50 Pennyfoot Street, Nottingham NG1 1GF (GB).

(74) Agents: MILLER, Thomas, Kerr et al.; BASF Aktiengesellschaft, D-67056 Ludwigshafen (DE).

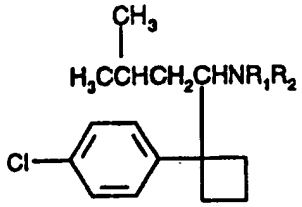
(81) Designated States: AL, AU, BG, BR, BY, CA, CN, CZ, GE, HU, ID, IL, JP, KR, KZ, LT, LV, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, US, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

**Published**
*With international search report.*
*Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.*

(54) Title: MEDICAL TREATMENT

(57) Abstract

A compound of formula (I) or a pharmaceutically acceptable salt thereof in which $R_1$ and $R_2$ are independently H or methyl (for example *N,N*-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl amine hydrochloride optionally in the form of its monohydrate) is used for lowering the uric acid level in humans, for example in humans suffering from or at risk of developing gout, hyperuricaemia or coronary heart disease.




(I)

*FOR THE PURPOSES OF INFORMATION ONLY*

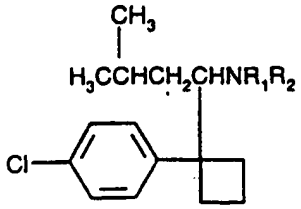
Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| AL | Albania | ES | Spain | LS | Lesotho | SI | Slovenia |
| AM | Armenia | FI | Finland | LT | Lithuania | SK | Slovakia |
| AT | Austria | FR | France | LU | Luxembourg | SN | Senegal |
| AU | Australia | GA | Gabon | LV | Latvia | SZ | Swaziland |
| AZ | Azerbaijan | GB | United Kingdom | MC | Monaco | TD | Chad |
| BA | Bosnia and Herzegovina | GE | Georgia | MD | Republic of Moldova | TG | Togo |
| BB | Barbados | GH | Ghana | MG | Madagascar | TJ | Tajikistan |
| BE | Belgium | GN | Guinea | MK | The former Yugoslav Republic of Macedonia | TM | Turkmenistan |
| BF | Burkina Faso | GR | Greece | ML | Mali | TR | Turkey |
| BG | Bulgaria | HU | Hungary | MN | Mongolia | TT | Trinidad and Tobago |
| BJ | Benin | IE | Ireland | MR | Mauritania | UA | Ukraine |
| BR | Brazil | IL | Israel | MW | Malawi | UG | Uganda |
| BY | Belarus | IS | Iceland | MX | Mexico | US | United States of America |
| CA | Canada | IT | Italy | NE | Niger | UZ | Uzbekistan |
| CF | Central African Republic | JP | Japan | NL | Netherlands | VN | Viet Nam |
| CG | Congo | KE | Kenya | NO | Norway | YU | Yugoslavia |
| CH | Switzerland | KG | Kyrgyzstan | NZ | New Zealand | ZW | Zimbabwe |
| CI | Côte d'Ivoire | KP | Democratic People's Republic of Korea | PL | Poland | | |
| CM | Cameroon | KR | Republic of Korea | PT | Portugal | | |
| CN | China | KZ | Kazakstan | RO | Romania | | |
| CU | Cuba | LC | Saint Lucia | RU | Russian Federation | | |
| CZ | Czech Republic | LI | Liechtenstein | SD | Sudan | | |
| DE | Germany | LK | Sri Lanka | SE | Sweden | | |
| DK | Denmark | LR | Liberia | SG | Singapore | | |
| EE | Estonia | | | | | | |

Medical Treatment

This invention relates to a method of lowering uric acid levels in the human body.

According to the present invention there is provided a method of lowering the uric acid level in the human body comprising administering to a human in need thereof a therapeutically effective amount of a compound of formula I



I

including enantiomers and pharmaceutically acceptable salts thereof, in which $R_1$ and $R_2$ are independently H or methyl, in conjunction with a pharmaceutically acceptable diluent or carrier.

The preparation and use of compounds of formula I, such as *N,N*-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine (or *N*-{1-[1-(4-chlorophenyl)-cyclobutyl]-3-methylbutyl}-*N,N*-dimethylamine) and salts thereof, in the treatment of depression is described in British Patent Specification 2098602. The use of compounds of formula I such as *N,N*-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine and salts thereof in the treatment of Parkinson's disease is described in European Patent Number 282206. The use of *N,N*-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine and salts thereof in the treatment of cerebral function disorders is described in US Patent 4939175. The use of *N,N*-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride in the treatment of obesity is described in European Patent Number 397831. A particularly preferred form of this compound is *N,N*-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride monohydrate (sibutramine hydrochloride monohydrate) which is described in European Patent Number 230742. The use of *N,N*-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine and salts thereof for improving the glucose tolerance of humans having Impaired Glucose Tolerance or Non-Insulin Dependent Diabetes Mellitus is described in published PCT application WO95/20949.

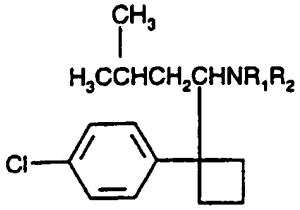
It may be appreciated by those skilled in the art that compounds of formula I may exist as salts with pharmaceutically acceptable acids. Examples of such salts include hydrochlorides, hydrobromides, sulphates, methanesulphonates, nitrates, maleates, acetates, citrates, fumarates, tartrates [eg (+)-tartrates, (-)-tartrates or mixtures thereof including racemic mixtures], succinates, benzoates and salts with amino acids such as glutamic acid. Compounds of formula I and their salts may exist in the form of solvates (for example hydrates).

It will be appreciated by those skilled in the art that compounds of formula I contain a chiral centre. When a compound of formula I contains a single chiral centre it may exist in two enantiomeric forms. The present invention includes the use of the individual enantiomers and mixtures of the enantiomers. The enantiomers may be resolved by methods known to those skilled in the art, for example by formation of diastereoisomeric salts or complexes which may be separated, for example, by crystallisation; via formation of diastereoisomeric derivatives which may be separated, for example, by crystallisation, gas-liquid or liquid chromatography; selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic oxidation or reduction, followed by separation of the modified and unmodified enantiomers; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support, for example silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where the desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step is required to liberate the desired enantiomeric form. Alternatively, specific enantiomers may be synthesised by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer to the other by asymmetric transformation.

Surprisingly, it has now been found that compounds of formula I have the ability to lower the uric acid level in the human body, and therefore have utility as uric acid-lowering agents. The presence of this activity indicates that compounds of formula I have use in the treatment and prophylaxis of conditions in which there is an elevated uric acid level, for example hyperuricaemia and gout. The compounds may also have utility in lowering the uric acid level in humans having or at risk of developing coronary heart disease.

Preferably, the present invention provides a method for the treatment and/or prophylaxis of gout or hyperuricaemia comprising the administration of a therapeutically effective amount of a compound of formula I in conjunction with a pharmaceutically acceptable diluent or carrier to a human in need thereof.

The present invention further comprises the use of a compound of formula I



I

including enantiomers and pharmaceutically acceptable salts thereof, in which $R_1$ and $R_2$ are independently H or methyl, in the manufacture of a medicament for lowering the uric acid level in humans, for example in humans suffering from or at increased risk of developing gout, hyperuricaemia or coronary heart disease. Preferably, the medicament is used in the treatment and/or prophylaxis of conditions in which there is an elevated uric acid level, for example hyperuricaemia or gout. The compounds may also have utility in lowering the uric acid level in humans having or at risk of developing coronary heart disease.

Specific compounds of formula I are *N,N*-dimethyl-1-[1-(4-chlorophenyl)-cyclobutyl]-3-methylbutylamine, *N*-[1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl]-*N*-methylamine, and 1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine including racemates, individual enantiomers and mixtures thereof, and pharmaceutically acceptable salts thereof. A preferred compound of formula I is *N,N*-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine or a salt thereof, for example the hydrochloride salt. A preferred form of this hydrochloride is its monohydrate.

The compound of formula I may be administered in any of the known pharmaceutical dosage forms. The amount of the compound to be administered will depend on a number of factors including the age of the patient, the severity of the condition and the past medical history of the patient and always lies within the sound discretion of the administering physician but it is generally envisaged that the dosag of the compound to be administered will be in the rang 0.1 to 50 mg preferably 1 to 30 mg per day given in one or more doses.

Oral dosage forms are the preferred compositions for use in the present invention and these are the known pharmaceutical forms for such administration, for example tablets, capsules, granules, syrups and aqueous or oil suspensions. The excipients used in the preparation of these compositions are the excipients known in the pharmacist's art. Tablets may be prepared from a mixture of the active compound with fillers, for example calcium phosphate; disintegrating agents, for example maize starch; lubricating agents, for example magnesium stearate; binders, for example microcrystalline cellulose or polyvinylpyrrolidone and other optional ingredients known in the art to permit tableting the mixture by known methods. The tablets may, if desired, be coated using known methods and excipients which may include enteric coating using for example hydroxypropylmethylcellulose phthalate. The tablets may be formulated in a manner known to those skilled in the art so as to give a sustained release of the compounds of the present invention. Such tablets may, if desired, be provided with enteric coatings by known methods, for example by the use of cellulose acetate phthalate. Similarly, capsules, for example hard or soft gelatin capsules, containing the active compound with or without added excipients, may be prepared by known methods and, if desired, provided with enteric coatings in a known manner. The contents of the capsule may be formulated using known methods so as to give sustained release of the active compound. The tablets and capsules may conveniently each contain 1 to 50 mg of the active compound.

Other dosage forms for oral administration include, for example, aqueous suspensions containing the active compound in an aqueous medium in the presence of a non-toxic suspending agent such as sodium carboxy-methylcellulose, and oily suspensions containing a compound of the present invention in a suitable vegetable oil, for example arachis oil. The active compound may be formulated into granules with or without additional excipients. The granules may be ingested directly by the patient or they may be added to a suitable liquid carrier (for example, water) before ingestion. The granules may contain disintegrants, eg an effervescent couple formed from an acid and a carbonate or bicarbonate salt to facilitate dispersion in the liquid medium.

Th therapeutically active compounds of formula I may be formulated into a composition which the patient retains in his mouth so that th active compound is administered through the mucosa of the mouth.

Dosage forms suitable for rectal administration are the known pharmaceutical forms for such administration, for example, suppositories with cocoa butter or polyethylene glycol bases.

Dosage forms suitable for parenteral administration are the known pharmaceutical forms for such administration, for example sterile suspensions or sterile solutions in a suitable solvent.

Dosage forms for topical administration may comprise a matrix in which the pharmacologically active compounds of the present invention are dispersed so that the compounds are held in contact with the skin in order to administer the compounds transdermally. A suitable transdermal composition may be prepared by mixing the pharmaceutically active compound with a topical vehicle, such as a mineral oil, petrolatum and/or a wax, e.g. paraffin wax or beeswax, together with a potential transdermal accelerant such as dimethyl sulphoxide or propylene glycol. Alternatively the active compounds may be dispersed in a pharmaceutically acceptable cream, gel or ointment base. The amount of active compound contained in a topical formulation should be such that a therapeutically effective amount of the compound is delivered during the period of time for which the topical formulation is intended to be on the skin.

The therapeutically active compound of formula I may be formulated into a composition which is dispersed as an aerosol into the patients oral or nasal cavity. Such aerosols may be administered from a pump pack or from a pressurised pack containing a volatile propellant.

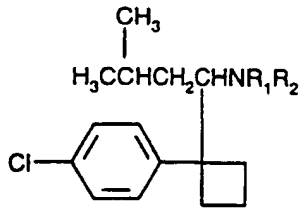
The therapeutically active compounds of formula I used in the method of the present invention may also be administered by continuous infusion either from an external source, for example by intravenous infusion or from a source of the compound placed within the body. Internal sources include implanted reservoirs containing the compound to be infused which is continuously released for example by osmosis and implants which may be (a) liquid such as an oily suspension of the compound t be infused for example in the form of a very sparingly water-soluble derivative such as a dodecanoate salt or a lipophilic ester or (b) solid in the form of an implanted support, for example of a synthetic resin or waxy material, for the compound to be infused. The support may be a single body containing all the compound or a

series of several bodies each containing part of the compound to be delivered. The amount of active compound present in an internal source should be such that a therapeutically effective amount of the compound is delivered over a long period of time.

In some formulations it may be beneficial to use the compounds of the present invention in the form of particles of very small size, for example as obtained by fluid energy milling.

In the compositions of the present invention the active compound may, if desired, be associated with other compatible pharmacologically active ingredients.

In another aspect, the invention provides a pharmaceutical composition for lowering the uric acid level in the human body, for example in humans suffering from or at increased risk of developing gout or hyperuricaemia, comprising a compound of formula I



I

including enantiomers and pharmaceutically acceptable salts thereof, in which $R_1$ and $R_2$ are independently H or methyl, in conjunction with a pharmaceutically acceptable diluent or carrier.

The efficacy of compounds of formula I in lowering plasma uric acid levels has been demonstrated in clinical trials as follows. It will be appreciated that a 10 mg dose or a 15 mg dose of sibutramine in the form of the hydrochloride monohydrate is equivalent to 8.37 mg or 12.55 mg of sibutramine as free base respectively.

Trial 1

In a clinically supervised trial, 485 mild to moderately obese patients were randomised to receive placebo, sibutramine hydrochloride monohydrate (10 mg) or sibutramine hydrochloride monohydrate (15 mg) orally once daily for 12 months. Reductions in uric acid l vels were observed at month 6, and were maintained at

month 12; the decreases in the sibutramine groups were greater than in the placebo group. The differences were statistically significant for the difference between sibutramine hydrochloride monohydrate 10 mg and placebo at month 6 and for the difference between sibutramine hydrochloride monohydrate 15 mg and placebo at month 6, endpoint and final assessment. The difference between sibutramine hydrochloride monohydrate 15 mg and 10 mg was also statistically significant at the final assessment ($p<0.05$). The data were analysed retrospectively according to weight loss.

Serum uric acid - Summary of mean percentage change from baseline to endpoint for long-term study (LOCF)

| Sub-group | Placebo | Sibutramine (10 mg) | Sibutramine (15 mg) |
|---|---|---|---|
| All patients | -1.7 | -5.6* | -7.8** |
| ≥5% weight loss | -3.9 | -9.5*** | -10.0*** |
| ≥10% weight loss | -4.7 | -14.1*** | -11.1*** |

'Sibutramine' and 'sib' mean sibutramine hydrochloride monohydrate

Baseline values (µmol/l):

Placebo 312.8; sib 10 mg 310.7; sib 15 mg 307.4

* $p \leq 0.05$ vs. all placebo

** $p \leq 0.01$ vs. all placebo

*** $p \leq 0.001$ vs. all placebo

Trial 2

In a further clinically supervised trial, 160 obese patients following a very low calorie diet were randomised to receive placebo or sibutramine hydrochloride monohydrate (10 mg) orally once daily for 12 months. Statistically significant reductions in uric acid levels were observed in the sibutramine group at month 6 and ndpoint compared to placebo. The data were analysed retrospectively according to weight loss.

Serum uric acid - Summary of mean percentage change from baseline to end-point for long-term study (LOCF)

| Sub-group | Placebo | Sibutramine (10 mg) |
|---|---|---|
| All patients | -11.1 | -19.0** |
| ≥5% weight loss | -22.5 | -21.7* |
| ≥10% weight loss | -28.2 | -27.1*** |

'Sibutramine' means sibutramine hydrochloride monohydrate

Baseline values (µmol/l):

Placebo 328.5; sibutramine 10 mg 335.4

* $p \leq 0.05$ vs. all placebo

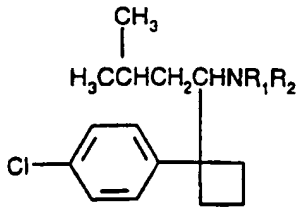
** $p \leq 0.01$ vs. all placebo

*** $p \leq 0.001$ vs. all placebo

The above results support the utility of compounds of formula I in lowering uric acid levels.

Claims

1. A method of lowering the uric acid level in the human body comprising administering to a human in need thereof a therapeutically effective amount of a compound of formula I



I

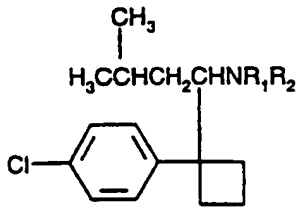
including enantiomers and pharmaceutically acceptable salts thereof in which $R_1$ and $R_2$ are independently H or methyl, in conjunction with a pharmaceutically acceptable diluent or carrier.

2. A method as claimed in claim 1 in which the human is suffering from gout or hyperuricaemia.

3. A method as claimed in claim 1 or 2 wherein the compound of formula I is *N,N*-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride.

4. A method as claimed in claim 1 or 2 wherein the compound of formula I is *N,N*-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride in the form of its monohydrate.

5. The use of a compound of formula I



I

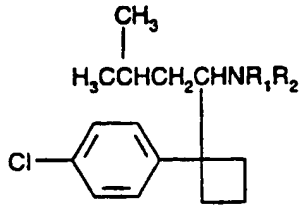
including enantiomers and pharmaceutically acceptable salts thereof in which $R_1$ and $R_2$ are independently H or methyl, in the manufacture of a medicament for lowering the uric acid level in humans.

6. The use as claimed in claim 5 in which the medicament is a medicament for the treatment of gout or hyperuricaemia.

7. The use as claimed in claim 5 or 6 in which the compound of formula I is *N,N*-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride.

8. The use as claimed in claim 5 or 6 in which the compound of formula I is *N,N*-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride monohydrate.

9. A pharmaceutical composition for lowering the uric acid level in the human body, comprising a therapeutically effective amount of a compound of formula I



I

including enantiomers and pharmaceutically acceptable salts thereof in which $R_1$ and $R_2$ are independently H or methyl, in conjunction with a pharmaceutically acceptable diluent or carrier.

10. A pharmaceutical composition as claimed in claim 9 in which the uric acid level is lowered in humans suffering from gout or hyperuricaemia.

11. A pharmaceutical composition as claimed in claim 9 or 10 in which the compound of formula I is *N,N*-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride.

12. A pharmaceutical composition as claimed in claim 9 or 10 in which the compound of formula I is *N,N*-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride monohydrate.

13. A method of prophylaxis of gout, hyperuricaemia or coronary heart disease in humans at increased risk of developing these conditions, comprising the administration of a therapeutically effective amount of a compound of formula I, as defined in claim 1, in conjunction with a pharmaceutically acceptable diluent or carrier to a human in need thereof.

14. The use of a compound of formula I, as defined in claim 5, in the manufacture of a medicament for the prophylaxis of gout, hyperuricaemia or coronary heart disease in humans at increased risk of developing these conditions.

15. A pharmaceutical composition for the prophylaxis of gout, hyperuricaemia or coronary heart disease in humans at increased risk of developing these conditions, comprising a therapeutically effective amount of a compound of formula I, as defined in claim 9, in conjunction with a pharmaceutically acceptable diluent or carrier.

# INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 97/05034

A. CLASSIFICATION OF SUBJECT MATTER

A 61 K 31/135

According to International Patent Classification (IPC) or to both national classification and IPC 6

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A 61 K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 95/20949 A1 (BOOTS PHARMACEUTICALS, INC.) 10 August 1995 (10.08.95), abstract, claims 10-12 (cited in the application). | 9-12, 15 |
| A | Claims 1-9, page 1, line 6 - page 2, line 13. | 1-8, 13,14 |
| X | WO 90/06110 A1 (THE BOOTS COMPANY PLC) 14 June 1990 (14.06.90), claims 7-8 (cited in the application). | 9-12, 15 |
| A | Abstract, claims 1-6. | 1-8, 13,14 |
| X | EP 0230742 A1 (THE BOOTS COMPANY PLC) 05 August 1987 (05.08.87), | 9-12, 15 |

[X] Further documents are listed in the continuation of box C. [ ] Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search
18 December 1997

Date of mailing of the international search report
-4. 02. 98

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+ 31-70) 340-3016

Authorized officer
MAZZUCCO e.h.

Form PCT/ISA/210 (second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 97/05034

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| | abstract, claim 2, page 3, lines 7-23 (cited in the application). | |
| A | Claim 10, page 3, lines 24-30. | 1-8, 13,14 |
| | -- | |
| X | EP 0339280 A2 (KAKEN PHARMACEUTICAL CO., LTD.) 02 November 1989 (02.11.89), abstract, page 2, lines 18-28. | 9-11, 15 |
| A | Claims 1-3. | 1-8, 13,14 |
| | -- | |
| X | EP 0282206 A1 (THE BOOTS COMPANY PLC) 14 September 1988 (14.09.88), abstract, claims 9,12 (cited in the application). | 9-12, 15 |
| A | Abstract, claims 1,2. | 1-8, 13,14 |
| | -- | |
| X | GB 2098602 A (THE BOOTS COMPANY PLC) 24 November 1982 (24.11.82), abstract, claim 15, claims 18,13 in connection with table 1, line 35 (cited in the application). | 9-11, 15 |
| A | Abstract. | 1-8, 13,14 |
| | -- | |
| X | US 4939175 A (UKAI, K. et al.) 03 July 1990 (03.07.90), column 1, lines 39-61 (cited in the application). | 9-11, 15 |
| A | Abstract, claim 1, column 1, line 66 - column 2, line 13. | 1-8,14 |
| | -- | |
| X | WO 94/00114 A1 (SEPRACOR INC.) 06 January 1994 (06.01.94), claims 10-17,27-34,46-53,66-73. | 9,10, 15 |
| A | Claims 1,8,9,18-26,35-45,54-65. | 1-8, 13,14 |
| | -- | |
| X | WO 94/00047 A1 (SEPRACOR INC.) 06 January 1994 (06.01.94), claims 10-17,27-34,46-53,66- | 9,10, 15 |

# INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 97/05034

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | 73.<br>Claims 1,8,9,18-26,35-45,54-65.<br>---- | 1-8,<br>13,14 |

# INTERNATIONAL SEARCH REPORT

Ir ternational application No.
PCT/EP 97/05034

**Box I** Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 1-4 and 13 are directed to a method of treatment of the human or animal body by therapy (Rule 39.1(iv)PCT) the search has been carried out and based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II** Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

## ANHANG

zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

## ANNEX

to the International Search Report to the International Patent Application No.

## ANNEXE

au rapport de recherche international relatif à la demande de brevet international n°

PCT/EP 97/05034 SAE 171952

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The Office is in no way liable for these particulars which are given merely for the purpose of information.

La présente annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche international visée ci-dessus. Les renseignements fournis sont donnés à titre indicatif et n'engagent pas la responsabilité de l'Office.

| Im Recherchenbericht angeführtes Patentdokument<br>Patent document cited in search report<br>Document de brevet cité dans le rapport de recherche | Datum der Veröffentlichung<br>Publication date<br>Date de publication | Mitglied(er) der Patentfamilie<br>Patent family member(s)<br>Membre(s) de la famille de brevets | Datum der Veröffentlichung<br>Publication date<br>Date de publication |
|---|---|---|---|
| WO A1 9520949 | 10-08-95 | AU A1 17362/95 | 21-08-95 |
| | | CA AA 2182620 | 10-08-95 |
| | | CN A 1144479 | 05-03-97 |
| | | IL A0 112515 | 08-12-95 |
| | | US A 5459164 | 17-10-95 |
| | | ZA A 9500814 | 03-08-95 |
| WO A1 9006110 | 14-06-90 | AT E 94385 | 15-10-93 |
| | | AU A1 46207/89 | 26-06-90 |
| | | AU B2 633589 | 04-02-93 |
| | | CA AA 2005524 | 29-05-90 |
| | | DE C0 68909219 | 21-10-93 |
| | | DE T2 68909219 | 13-01-94 |
| | | DK A0 1776/90 | 26-07-90 |
| | | DK A 1776/90 | 13-09-90 |
| | | EP A1 397831 | 22-11-90 |
| | | EP B1 397831 | 15-09-93 |
| | | IE B 61928 | 30-11-94 |
| | | IL A0 92406 | 17-09-90 |
| | | IL A1 92406 | 31-07-95 |
| | | JP T2 2503682 | 01-11-90 |
| | | JP B4 6102628 | 14-12-94 |
| | | ZA A 8909058 | 29-08-90 |
| | | US A 5436272 | 25-07-95 |
| EP A1 230742 | 05-08-87 | AT E 56942 | 15-10-90 |
| | | AU A1 66442/86 | 18-06-87 |
| | | AU B2 601167 | 06-09-90 |
| | | CA A1 1266278 | 27-02-90 |
| | | CN A 86108547 | 19-08-87 |
| | | CN B 1016245 | 15-04-92 |
| | | CS A2 8609305 | 15-02-88 |
| | | CS B2 [illegible] | 14-10-88 |
| | | DD A5 [illegible] | 21-12-88 |
| | | DE C0 3674570 | 21-10-90 |
| | | DK A0 5857/86 | 05-12-86 |
| | | DK A 5857/86 | 18-06-87 |
| | | DK B1 170770 | 15-01-96 |
| | | EG A 17770 | 30-03-91 |
| | | EP B1 230742 | 26-09-90 |
| | | FI A0 865030 | 10-12-86 |
| | | FI A 865030 | 18-06-87 |
| | | FI B 90413 | 29-10-93 |
| | | FI C 90413 | 10-02-94 |
| | | GB A0 8531071 | 29-01-86 |
| | | GB A1 2184123 | 17-06-87 |
| | | GB B2 2184123 | 18-10-89 |
| | | GR T3 3001069 | 30-03-92 |
| | | HR A1 930745 | 30-06-95 |
| | | HU A2 45964 | 28-09-88 |
| | | HU B 201901 | 28-01-91 |
| | | IE B 59429 | 23-02-94 |
| | | IL A0 80934 | 16-09-87 |
| | | IL A1 80934 | 26-07-90 |
| | | IN A 163129 | 13-08-88 |
| | | JP A2 62155240 | 10-07-87 |
| | | JP B4 1044176 | 26-09-89 |
| | | KR B1 9408913 | 28-09-94 |
| | | LT A3 [illegible] | 15-02-94 |
| | | NO A0 865067 | 16-12-86 |
| | | NO A 865094 | 18-06-87 |
| | | NO B 165540 | 19-11-90 |
| | | NO C 165540 | 27-02-91 |
| | | NZ A 218578 | 26-04-89 |
| | | PH A 24481 | 12-09-88 |
| | | PL A1 263020 | 12-05-88 |
| | | PL B1 149519 | 28-02-90 |
| | | PT A [illegible] | 01-01-87 |
| | | PT B [illegible] | 14-05-89 |

./.

| | | | | | |
|---|---|---|---|---|---|
| | | | PL | A1 | 240079 |
| | | | PL | B1 | 1362[illegible] |
| | | | PL | B1 | 1391[illegible] |
| | | | PT | A | 7458[illegible] |
| | | | PT | B | 7458[illegible] |
| | | | RO | F | 8480[illegible] |
| | | | RO | B1 | 9943[illegible] |
| | | | SE | A | 8202[illegible] |
| | | | SE | B | 4[illegible] |
| | | | SE | C | 4[illegible] |
| | | | SG | A | 6[illegible] |
| | | | SI | AB | 8[illegible] |
| | | | SI | AB | 8[illegible] |
| | | | SU | A | 1[illegible] |
| | | | SU | A | 1[illegible] |
| | | | US | A | 4[illegible] |
| | | | US | A | 4[illegible] |
| | | | US | A | 4[illegible] |
| | | | US | A | 4[illegible] |
| | | | US | A | 4[illegible] |
| | | | US | B1 | 4[illegible] |
| | | | YU | A | [illegible] |
| | | | YU | A | 750/[illegible] |
| | | | YU | B | 44[illegible] |
| | | | YU | B | 44[illegible] |
| | | | ZA | A | 8201[illegible] |
| | | | ZM | A | 24/[illegible] |
| | | | ZW | A | 49/[illegible] |
| | | | US | A | 4443449 |

| | | | | | |
|---|---|---|---|---|---|
| US A | 4939175 | 03-07-90 | EP | A2 | 339280 |
| | | | EP | A3 | 339280 |
| | | | JP | A2 | 1-50[illegible]15 |
| WO A1 | 9400114 | 06-01-94 | AU | A1 | 45428/93 |
| | | | EP | A1 | 647134 |
| | | | EP | A4 | 647134 |
| | | | JP | T2 | 8500093 |
| WO A1 | 9400047 | 06-01-94 | AU | A1 | 45429/93 |
| | | | EP | A1 | 708659 |
| | | | EP | A4 | 708659 |
| | | | JP | T2 | 7508261 |

| | | | | | |
|---|---|---|---|---|---|
| | | | PL | A1 | 12-09-83 |
| | | | PL | B1 | 28-02-86 |
| | | | PT | A | 01-12-86 |
| | | | PT | B | 01-04-87 |
| | | | RO | F | 23-12-87 |
| | | | RO | B1 | 30-09-94 |
| | | | SE | A | 30-06-86 |
| | | | SE | B | 25-11-87 |
| | | | SE | C | 07-12-87 |
| | | | SG | A | 17-03-88 |
| | | | SI | AB | 19-02-90 |
| | | | SI | AB | 30-06-96 |
| | | | SU | A | 30-06-97 |
| | | | SU | A | 30-02-89 |
| | | | US | A | 28-05-89 |
| | | | US | A | 11-06-85 |
| | | | US | A | 24-05-88 |
| | | | US | A | 30-08-88 |
| | | | US | A | 21-02-89 |
| | | | US | A | 21-02-89 |
| | | | US | B1 | 11-05-93 |
| | | | YU | A | 31-08-88 |
| | | | YU | A | 31-08-95 |
| | | | YU | B | 30-04-90 |
| | | | YU | B | 30-06-90 |
| | | | ZA | A | 30-03-83 |
| | | | ZM | A | 21-07-83 |
| | | | ZW | A | 03-11-82 |
| | | | US | A | 17-04-84 |

| | | | | | |
|---|---|---|---|---|---|
| US A | 4939175 | 03-07-90 | EP | A2 | 02-11-89 |
| | | | EP | A3 | 19-09-90 |
| | | | JP | A2 | 05-10-89 |
| WO A1 | 9400114 | 06-01-94 | AU | A1 | 24-01-94 |
| | | | EP | A1 | 12-04-95 |
| | | | EP | A4 | 30-07-97 |
| | | | JP | T2 | 09-01-96 |
| WO A1 | 9400047 | 06-01-94 | AU | A1 | 24-01-94 |
| | | | EP | A1 | 01-05-96 |
| | | | EP | A4 | 20-08-97 |
| | | | JP | T2 | 14-09-95 |